REMARKS

Status of the Claims.

Claims 1-22 are pending with entry of this amendment. Claims 1-22 are amended herein to clarify that the library is a composition, e.g., that includes all members of the library as opposed to individual nucleic acids. No new matter is added by this amendment (See, e.g., the abstract) and Applicants respectfully request that the amendments be entered.

Claims 1-22 were rejected for alleged obviousness and alleged anticipation. Applicants traverse all rejections for the reasons of record, and, additionally, for the reasons noted herein.

Brief discussion of the invention

Perhaps the Examiner is not working with a current copy of the claims because it appears that the rejection is based on a couple of misconceptions about the invention. See, e.g., paragraph 3 on page 10 of the response, where it is alleged that the claims do not recite that each of the constructs binds to a specified transcription factor. See, e.g., 2nd paragraph on page 26 of Office Action alleging that Applicants arguments rely on an unclaimed aspect of the invention, the alleged unclaimed aspect being two variable regions. The description below clarifies these misconceptions.

Claim 1 states (emphasis added):

> A composition comprising a library of nucleic acid constructs, **each construct comprising**:
> a cis-element sequence comprising one or more copies of **a cis element to which a specified transcription factor is known to bind**, the cis element sequence **varying** within the library of nucleic acid constructs;
> a promoter sequence 3' relative to the cis element sequence;
> a reporter sequence 3' relative to the promoter sequence, the reporter sequence comprising a **variable sequence** that varies within the library of nucleic acid constructs;
> wherein each cis element sequence corresponds to a **different** reporter sequence within the library of nucleic acid constructs.

Each construct of the claimed library comprises a cis element and that cis element is known to bind a specified transcription factor. The construct may include other things and the cis element may contain other sequences but **every construct** in the library **must include** a "cis element to which a specified transcription factor is known to bind." The

language is plain; each construct must contain at least three elements: the cis element, the promoter and the reporter, all with their respective limitations. Each construct may include other things in addition to those three elements, hence the use of the term comprising; however, a construct without those elements may not be included in the library. This type of library is not present in the prior art.

The Action also alleged that Applicants relied on features not claimed in their argument that the constructs taught in the cited art must have two variable regions. Applicants respectfully point out that in addition to the variable reporter sequence, the cis element region must also have a variable region as claimed. The claims refer to it as "varying within the library." Therefore, there is a "variable" region and a "varying" region, or two variable regions. The prior art does not contain or suggest a library wherein each construct is as claimed, including two varying regions that correspond to each other.

THE CLAIMS ARE NOT OBVIOUS OVER THE ART

The Examiner rejected claims 1-22 under 35 U.S.C. §103(a) for alleged obviousness over Kauffman in view of Morris. Applicants traverse. Claims 1-22 were also rejected under 35 U.S.C. §103(a) for alleged obviousness over Li in view of Morris. Applicants traverse and amend the claims for clarity.

A finding of obviousness requires a determination of whether "the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time was made to a person having ordinary skill in the art to which said subject matter pertains." 35 USC § 103(a). As the Federal Circuit has repeatedly indicated, this inquiry ultimately involves determining "whether a person of ordinary skill would have been motivated to combine the prior art to achieve the claimed invention and whether there would have been a reasonable expectation of success in doing so." *Dystar Textilfarben GmbH v. C.H. Patrick Co.* 80 USPQ2d 1641 at 1645 (Fed. Cir. 2006). The determination of the questions of motivation and expectation of success are based upon a four part factual inquiry:

(1) the scope and content of the prior art;

(2) the differences between the claimed invention and the prior art;

(3) the level of ordinary skill in the art; and,

(4) consideration of secondary indicia of non-obviousness.

Dystar, *id*, quoting *Graham v. John Deere Co.*, 383 US 1, 17 [148 USPQ 459] (S. Ct. 1966). The Supreme Court recently reaffirmed the factual analysis established in *Graham v. John Deere Co.*, cautioning that the question of motivation to combine the prior art must be approached with "common sense," rather than as a rigid formula:

> When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill in the art has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense.

KSR International Co. V. Teleflex inc. et al. 550 U. S. ____ (2007) slip opinion page 6.

The Examiner alleged that Kauffman and Morris teach a library of nucleic acid constructs as claimed and that because both references address expression methods and a need for high throughput methods it was obvious to combine them to produce the claimed invention. However, this argument does not recognize the fact that **each** construct in the claimed library comprises a cis element "to which a **specified** transcription factor is **known** to bind" and that each construct comprises two corresponding variable regions: each cis element/transcription factor pair corresponds to a different reporter sequence. Therefore the claims are not obvious over Kauffman and Morris.

The Examiner alleged that Li either anticipates the claimed invention or in the alternative renders it obvious in view of Morris. However, Li does not teach a composition comprising the library as claimed. The constructs in Li are individual constructs not contained within a composition. And although Li mentions different reporters that can be used, the individual constructs of Li that are alleged to be the "library" all comprise the same reporter, see, e.g., Figure 4. No correspondence between a particular cis element and reporter is found in Li and even when combined with Morris, no composition comprising a library as claimd can be found. Therefore, the claims are not obvious over or anticipated by Li.

Both combinations of references fail to establish the Office's burden of persuasion on the issue of obviousness *vel non*. Indeed, no case for obviousness can properly be made out at all. The combination of references (A) entirely fail to teach the elements of

the claim; and (B) no specific "common sense" motivation exists in the prior art for the combination. In addition, as will be discussed in considering the differences between the prior art and the invention and the level of skill in the art, no expectation of success in the proposed combination, derived from the prior art, can possibly be made out for the proposed combination. Complete consideration of the Graham factors and the legal standards of motivation and expectation of success clearly establish the *non-obvious* nature of the invention. The Graham factors are examined below for each of the art combinations relied upon in the rejection.

The Claims are not Obvious Over Kauffman and Morris

The scope and content of the prior art

In considering the scope and content of the prior art, a first basic requirement for establishing obviousness is that the combination of references must actually teach all of the elements of the claims. MPEP 2143.03. The combination of references in the rejection entirely fails to meet this most basic of factual requirements for establishing obviousness.

The elements of the claim are not taught in Kauffman and Morris

The rejection entirely failed to address an element of the claims that is not found in the prior art, e.g., the fact that "**each construct**" comprises a cis element that is "**known to bind**" to a "**specified transcription factor**." This was not addressed in the rejection and cannot be because this element, although properly claimed as described above, is not found in the prior art. The prior art therefore, does not teach each and every element of the claims.

The Action alleged that Kauffman inherently discloses all the members of the library as claimed. While it may be true that all the sequences of the claimed library are included in Kauffman, the claimed library contains only those that comprise the following: a cis-element to which a specified transcription factor is known to bind, which cis element sequence varies within the library; a promoter, a variable reporter sequence 3' relative to the promoter sequence, the reporter sequence comrising a variable sequence that varies within the library of nucleic acid constructs; wherein each cis element sequence corresponds to a different reporter sequence within the library.

Applicants acknowledge that Kauffman discloses a randomized group of sequences that includes all possible sequences of a certain length. However, Kauffman must give some reason for selecting the same group of constructs as claimed, otherwise how would someone of skill know which of the nucleic acids of Kauffman to include in a library as claimed. Although Kauffman, in some sense, discloses all sequences, it does not render the claimed invention obvious because it does not provide guidance as to how to select out those nucleic acids as claimed or any reasons why one would do so.

According to the Federal Circuit in *In re Newell,* reliance on an alleged inherent teaching is not sufficient to support an obvious rejection. "A retrospective view of inherency is not a substitute for some teaching or suggestion that supports the selection and use of the elements in the particular claimed combination. In deciding that a novel combination would have been obvious, there must be supporting teaching in the prior art; for that which may be inherent is not necessarily known, and obviousness cannot be predicated on what is unknown." See, *In re Newell*, 891 F.2d 899, 13 U.S.P.Q.2d 1248, 1250 (Fed. Cir. 1989). A teaching that a nucleic acid between 5 and 20 nucleotides in length of any combination of naturally occurring nucleotides, while technically including every possible nucleic acid of that length, is not sufficient to teach a particular subset of nucleic acids because it does not teach how or why one of skill would identify and select that subset, e.g., a group of cis acting sequences that each bind to a specified transcription factor as required in the claimed invention. So even if the claimed nucleic acid constructs are all inherently included in the nucleic acids of Kauffman, there is no teaching regarding how to select and identify the cis acting sequences and the transcription factors to which they bind. In the claimed library, **each** construct includes a cis element that is **known** to bind to a **specified** transcription factor. The cis elements in Kauffman do not all bind to transcription factors. Furthermore, if any of the cis elements inherently bind a transcription factor, that factor is unknown, not a specified factor as claimed. These defects are not in any way addressed by the combination with Morris. Therefore, the cited references do not teach each and every element of the claimed invention and cannot render it obvious.

The rejection relies on Morris to teach a variable reporter, because clearly, the nucleic acids in Kauffman do not contain two corresponding variable regions. Morris does

not teach two corresponding variable sequences any more than Kauffman does. Morris, if anything, teaches a variable nucleic acid tag that hybridizes to another nucleic acid. To teach every element of the claimed invention, the references must teach a single nucleic acid construct comprising **two corresponding variable regions**. When this argument was made previously, it was deemed unpersuasive because of an apparent belief that the claimed constructs do not contain two variable regions. As described above, the claims do in fact contain two variable regions, the cis element "varying within the library" and the variable reporter sequence. The fact that one reference has a variable region in one nucleic acid and another reference teaches a variable region in an unrelated nucleic acid, both of which are used in different ways cannot be combined to produce one nucleic acid with two variable regions that vary dependently or correspond to each other as claimed, e.g., to allow identification of cis acting elements and transcription factors. Neither reference teaches the addition of a variable reporter to a nucleic acid that already has a variable cis element region. The cited references in combination do not teach each and every element of the claims and the rejection must be withdrawn.

The Office action appears to consider this a product by process claim and states that the product is the same and therefore it does not matter whether the transcription factors are specified beforehand – that this is a process step that does not result in a different product. Applicants respectfully disagree. Specifying which transcription factors the cis elements in the library recognize also leads to a different product; a library of nucleic acids known to bind to a particular group of transcription factors in contrast to the library of Kauffman in which it is not known which constructs bind to transcription factors and if so, which transcription factors.

Furthermore, the Office argued that the reporters of Kauffman correspond to the cis element but they actually correspond to a randomized sequence – not to a specified transcription factor or cis element sequence. This is not correspondence as claimed, e.g., each different cis element corresponding to a different reporter. Therefore, the combination of Kauffman and Morris does not anticipate or render obvious the claimed invention.

No specific motivation exists for the combination of Kauffman and Morris

The Federal Circuit has articulated a subsidiary factor to be considered when evaluating the scope and content of the prior art, i.e., whether the combination of references is motivated by the prior art, and not simply by Applicants disclosure. *Dystar Textilfarben GmbH v. C.H. Patrick Co.* 80 USPQ2d 1641 at 1645 (Fed. Cir. 2006), quoting *Graham v. John Deere Co.* 383 U.S. at 36.

The rejection completely fails to show the motivation needed to modify the library of Kauffman from a randomized library to a known library wherein each construct binds to a known transcription factor. Furthermore, it fails to show a specific motivation for a randomized library to have the variable reporter sequence of Morris. Applicants question why would one skilled in the art want to combine the randomized library of Kauffman with the reporter genes of Morris? It is only with reference to Applicants own disclosure and Applicants' library of constructs that one sees the need to use a variable reporter that corresponds to a specific cis-element/transcription factor binding pair. Looking at Kauffman or Morris, this need, e.g., the need to have a library that can be used to identify transcription factors, does not arise, nor does any motivation arise, because the random constructs of Kauffman would not benefit from the variable reporters of Morris. The combination is motivated by the correlation between specific transcription factors and specific reporters, which disclosure is only found in the instant application. Therefore, there would be no reason to combine a variable reporter with a randomized unknown library. Unless each member of the library is specified as claimed, then the variable reporter is useless.

The Examiner relied on a quote in Kauffman stating that, "nucleic acid chips and automated detection procedures are particularly advantageous in high-throughput screening procedures **for identifying cis-acting nucleic acid elements**." (emphasis added). The claimed invention relies on the existence of previously identified cis-acting nucleic acid elements. Therefore, the quote cannot provide a motivation to produce the claimed invention. If anything, the quote provides a motivation to automate the detection for a library of probes for identifying previously unknown cis acting nucleic acid elements. The claimed libraries comprise previously identified cis acting elements that bind to specified transcription factors, e.g., for identifying when those specified transcription factors are

present in a cell sample or with what other factors the specified transcription factors are interacting. Therefore, whatever motivation is espoused by Kauffman is meaningless to the claimed invention. It motivates, if anything, a change in a procedure that is irrelevant to the present claims.

Furthermore, none of the motivations articulated by the Action have shown a design, need or pressure to solve a problem for which there are a finite number of solutions. The problem solved by any combination of Kauffman and Morris, e.g., how to identify cis elements, is not the same as the problem solved by the claimed invention, e.g., how to detect transcription factor interactions. In addition, the number of possibilities for solution of either of the problems is infinite, complicated, and unpredictable. Therefore no motivation or expectation of success exists, making the success of Applicants in designing this library the product if innovation, not common sense as required by KSR to uphold an obviousness rejection.

The differences between the claimed invention and the prior art

The second Graham factor relates to the differences between the claimed invention and the prior art. The prior art, as discussed above, relates only to randomized libraries with no identified binding specificity. In contrast, the *claimed* invention relates to a library of nucleic acids specifically selected for their ability to bind to a specified transcription factor.

For example, each transcription factor associated with the claimed invention is "specified," e.g., explicitly named or stated. See, e.g., Merriam Webster online dictionary. Although the claims to do not themselves explicitly list each transcription factor that binds to a cis element of the claimed library, they require that each cis element be known to bind to a specified transcription factor. It does not matter which transcription factors are specified (the library works with any number of different transcription factors), as long as the transcription factors are known to bind to a particular cis-elements, so that they can be identified using the variable reporter that corresponds to that cis element.

The requirement that the cis elements bind to explicity stated transcription factors is not met in the prior art. The so called "cis elements" of the prior art are only possible cis elements. They are not each "known to bind" to a "specified transcription

factor." The cis elements of the prior art are merely sequences for which one hopes to determine binding preferences. The sequences are not known to bind to anything; they have not been identified or selected, nor has anyone determined whether they bind to a transcription factor, much less specified the transcription factor to which they bind. The libraries of the claimed invention contain a sequence that has been previously determined to bind to a specified, e.g., certain or specific, transcription factor and only those cis elements that bind to specified transcription factors, e.g., those of interest, are included in the libraries as claimed. This element has not been shown by the Office and therefore the claims cannot be rejected for obviousness over Kauffman and Morris.

The level of ordinary skill in the pertinent art

While most practioners in the art, e.g., those studying and using transcription factors, nucleic acid libraries, and the like, are quite skilled, there is still no reason for anyone to put the variable reporters of Morris into the randomized library of Kauffman. The Action alleged that a reasonable expectation of success for the Kauffman and Morris combination exists because the mere substitution of one reporter for another would lead to the same predictable result, namely the identification of the cis elements. Applicants respectfully point out that the cis elements of the claimed library are already identified, e.g., known to bind to a specified transcription factor, so Applicants question how such a result could be applicable to or provide an expectation of success for the claimed invention in which all cis-elements are already known. The idea of any expectation of success is very vague in this instance. Of course, the techniques needed to make each of the claimed constructs are known in the art and the skill in the art is certainly such that it could be done. The inventive concept is the selection of the particular combination of elements claimed. The problem with the rejection is that the combination of Kauffman and Morris would yield a different type of library that could not be as successful a library as claimed. For example, without the correlation between each cis element and a specified transcription factor to which it is known to bind, there is no point in correlating a reporter to the cis element. Therefore, although one of skill could easily have made such constructs, there is nothing in the art to motivate one to do so and if one did try to combine the two references, it would not have resulted in a library as claimed.

In short, the combination of Kauffman and Morris completely fails to establish a case for obviousness. The combination of references does not even remotely provide the limitations of the claims; there is no *specific* motivation to make the combination of references supposed, and there was, plainly, no expectation that the nucleic acids of Kauffman combined with the techniques of Morris could result in libraries as claimed, prior to Applicants' invention. Applicants ask a simple question: which of the 10^{13} sequences of Kauffman are to be used with the reporters of Morris to provide a library specific to transcription factors as claimed? With no correspondence between particular cis-element/transcription factor binding pairs and the variable reporters, the reporters of Morris serve no purpose for the libraries of Kauffman. Therefore, no expectation of success is provided in the references for the nucleic acids of Kauffman and the variable tags of Morris to work as do the libraries of the claimed invention. The rejection completely fails to state a case for obviousness and must be withdrawn.

The Claims are not Obvious Over Li and Morris

Claims 1-22 were rejected under 35 U.S.C. §103(a) for alleged obviousness over Li in view of Morris. Applicants traverse, but amend the claims herein for clarity. The claims are amended herein to clarify exactly what is meant by a library, e.g., in the claimed invention, a library is a group of nucleic acids constructs contained within a composition. That should clarify that Li and/or Li and Morris do not anticipate or render obvious the claimed invention because the constructs in Li are individual constructs in separate microwells.

As discussed above, a finding of obviousness requires a determination of whether the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art. This determination is informed by the Graham factors as discussed above and applied to Li and Morris below.

The scope and content of the prior art

As discussed above, a first basic requirement for establishing obviousness is that the combination of references must actually teach all of the elements of the claims.

MPEP 2143.03. The combination of references in the rejection entirely fails to meet this most basic of factual requirements for establishing obviousness.

The elements of the claim are not taught in Li and Morris

The constructs of Li are not a library or a collection. They are merely individual items. A library is a group or collection, e.g., in one location used together for a single purpose. Applicants herein amend the claims to clarify this point, e.g., that the constructs claimed are a part of a group in the same composition. This clarifies the structural aspect of the constructs all being grouped together physically into a single composition. The correspondence between the variable reporter and the various cis elements of the library allow this grouping into a single composition. For example, every cis element is associated with or corresponds to a different reporter. The constructs of Li are not grouped together in this manner, nor would such a group be a successful because Li does not teach a correspondence between the various cis elements and reporters as claimed. They are aware of the fact that different reporters exist and that different transcription factors exist, but they do not combine them in this manner. Without the particular correspondence provided by the claimed library, the grouping into a single composition does not make sense.

The probes in Li have not been collected into a library that is used together as a group. Although Li may discuss different reporters, they do not identify, select, or group together any particular probes having the claimed characteristics, e.g., a set of probes that have known cis elements that vary dependently with the reporter as claimed. Li may show an individual construct with a cis-element that binds to a known transcription factor and a reporter that allegedly corresponds to it, but they do not have a collection of constructs that have different cis elements binding to different known transcription factors and **different** reporters that correspond to the cis elements. At most they have multiple individual constructs – there is no grouping showing the different cis elements corresponding to the different reporters. Figure 4 is relied upon by the Office, but Figure 4 shows that every construct has the same reporter. Where is a group or library of constructs with the claimed elements, e.g., in a single composition as claimed?

The rejection relies on Morris to teach a variable reporter as described above in the response to the previous rejection. Morris does not teach two corresponding variable

sequences any more than Li does. Morris, if anything, teaches a variable nucleic acid tag that hybridizes to another nucleic acid. To teach every element of the claimed invention, the references must teach a group of nucleic acid constructs, each comprising **two corresponding variable regions**. When this argument was made previously, it was deemed unpersuasive because of an apparent belief that the claimed constructs do not contain two variable regions. As described above, the claims do in fact contain two variable regions, the cis element "varying within the library" and the variable reporter sequence. The fact that one reference has a variable region in one nucleic acid and another reference teaches a variable region in an unrelated nucleic acid, both of which are used in different ways cannot be combined to produce a group of nucleic acids, each with two variable regions that vary dependently or correspond to each other as claimed, e.g., to allow simultaneous identification of multiple transcription factors. Neither reference teaches the addition of a variable reporter to a nucleic acid that already has a variable cis element region. The cited references in combination do not teach each and every element of the claims and the rejection must be withdrawn.

No specific motivation exists for the combination of Li and Morris

In addition to the obvious failure to teach every element of the claimed invention, e.g., the combination of the library into a single composition, no motivation for combining Li and Morris into the claimed composition is present in the prior art. There is nothing in Li or Morris to suggest or motivate the combination of references at issue. Furthermore, none of the motivations articulated by the Action show a design, need or pressure to solve a problem for which there are a finite number of solutions. Therefore no motivation or expectation of success exists, making the success of Applicants in designing this library the product o innovation, not common sense as required by KSR to uphold an obviousness rejection.

The differences between the claimed invention and the prior art

The second Graham factor relates to the differences between the claimed invention and the prior art. The prior art, as discussed above, relates only to individual sequences that bind to transcription factors. In contrast, the *claimed* invention relates to a

composition or mixture comprising multiple nucleic acids specifically selected for their ability to bind to different specified transcription factors and their ability to detect multiple transcription factors simultaneously due to the fact that every different transcription factor/cis element pair corresponds to a different reporter sequence.

Because the constructs of Li do not have reporters that vary to provide each cis-element a different reporter, see, e.g., Figure 4, there would be no motivation to combine them into one composition, e.g., one that could be used to simultaneously identify multiple transcription factors in a single sample. Applicants note that in pointing to uses for the claimed libraries they merely wish to highlight the structural differences between the libraries of the prior art and the claimed libraries. For example, the constructs of the invention are grouped into a composition while those of the prior art are not.

The combination as claimed is not present in the art. Therefore, the claims are not obvious over Li and Morris.

The level of ordinary skill in the pertinent art

As discussed above, the level of skill in the art is high. While anyone of skill in the art would be aware of the techniques needed to create each of the individual nucleic acids present in the claimed libraries, it is the combination that is novel and the Action has not stated any expectation of success that one of skill in the art would have had for such a combination. Therefore, one of skill would not have combined Li and Morris and had no expectation of success for doing so.

In short, the combination of Li and Morris completely fails to establish a case for obviousness. The combination of references does not even remotely provide the limitations of the claims and there is no *specific* motivation to make the combination of references supposed.

35 U.S.C. §102.

The claims were rejected under 35 U.S.C. §102(b) as allegedly anticipated by Li, or in the alternative rendered obvious. In order for a reference to anticipate an invention, the reference must teach each and **every** element of the claimed invention. In order for a reference to anticipate an invention, anticipation requires that "all limitations of the claim are

found in the reference, or 'fully met' by it." *Kalman v. Kimberly-Clark Corp.*, 218 USPQ 781, 789 (Fed. Cir. 1983).

As discussed above, Li does not teach a compoisition comprising a library of constructs as claimed. Therefore, Li does not teach every element of the claimed invention and cannot anticipate the claimed invention.

CONCLUSION AND REQUEST FOR EXAMINER INTERVIEW WITH SUPERVISING EXAMINER

The claims are in condition for allowance. A notice of allowance at an early date is, therefore respectfully requested. In the event that any issues of substance are believed to remain, Applicants respectfully request an Examiner Interview with Examiner Epperson and a Supervising Patent Examiner.

If the claims are deemed not to be in condition for allowance after consideration of this Response, please telephone the undersigned at (510) 337-7871 to schedule an interview.

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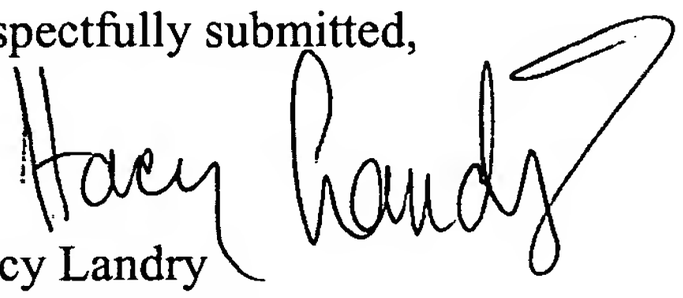
Respectfully submitted,



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Attachments:

1) A petition to extend the period of response for **3** months;
2) A transmittal sheet;
3) A receipt indication postcard